(50)

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ US

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty.

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference 31144
International application No. PCT/IL2006/000059	International filing date *(day/month/year)* 15 January 2006 (15/01/2006)	(Earliest) Priority date *(day/month/year)* 13 January 2005 (13/01/2005)

Title of invention
MULTI-DIMENSIONAL IMAGE RECONSTRUCTION AND ANALYSIS FOR EXPERT-SYSTEM DIAGNOSIS

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*	
Spectrum Dynamics LLC 30 Ramland Road South Orangeburg, NY 10962 USA	Telephone No. Facsimile No. Teleprinter No. Applicant's registration No. with the Office
State *(that is, country)* of nationality: US	State *(that is, country)* of residence: US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

ROUSSO Benny
12 Henri Bergson Street
75801 Rishon-LeZion
Israel

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Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

DICKMAN Dalia
175 Moshav Manof
20184 Doar-Na Misgav
Israel

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
IL	IL

☒ Further applicants are indicated on a continuation sheet.

Sheet No. .2

International application No.
PCT/IL2006/000059

Continuation of Box No. II **APPLICANT(S)**

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

NAGLER Michael
4 Avshalom Haviv Street
69495 Tel-Aviv
Israel

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IL	IL

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

VALLABHAJOSULA Shankar
73 Iselin Terrace
Larchmont, NY 10538
USA

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
IN	US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

☐ Further applicants are indicated on another continuation sheet.

Sheet No. ..3

International application No. PCT/IL2006/000059

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is [X] agent [ ] common representative

and [X] has been appointed earlier and represents the applicant(s) also for international preliminary examination

[ ] is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked

[ ] is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*	
EHRLICH, Gal PRTSI, Inc. P.O. Box 16446 Arlington, Virginia 22215	Telephone No. (703)598-7851 Facsimile No. (703)415-4864 Teleprinter No. Agent's registration No. with the Office

[ ] **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination **to start on the basis of:**

[ ] the international application as originally filed

the description [ ] as originally filed
[X] as amended under Article 34

the claims [ ] as originally filed
[ ] as amended under Article 19 (together with any accompanying statement)
[X] as amended under Article 34

the drawings [X] as originally filed
[ ] as amended under Article 34

2. [ ] The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.
3. [ ] Where the IPEA wishes to start the international preliminary examination at the same time as the international search in accordance with Rule 69.1(b), the applicant requests the IPEA **to postpone** the start of the international preliminary examination until the expiration of the applicable time limit under Rule 69.1(d).
4. [ ] The applicant expressly wishes the international preliminary examination **to start earlier** than at the expiration of the applicable time limit under Rule 54*bis*.1(a).

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

[X] which is the language in which the international application was filed
[ ] which is the language of a translation furnished for the purposes of international search
[ ] which is the language of publication of the international application
[ ] which is the language of the translation (to be) furnished for the purposes of international preliminary examination

Box No. V ELECTION OF STATES

The filing of this demand constitutes the election of all Contracting States which are designated and are bound by Chapter II of the PCT.

Sheet No. . .4

International application No.
PCT/IL2006/000059

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

			For International Preliminary Examining Authority use only: received	not received
1. translation of international application	:	sheets	☐	☐
2. amendments under Article 34	:	16 sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:	sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:	sheets	☐	☐
5. letter	:	3 sheets	☐	☐
6. other *(specify)*	:	sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ original separate power of attorney
3. ☐ original general power of attorney
4. ☐ copy of general power of attorney; reference number, if any:
5. ☐ statement explaining lack of signature
6. ☐ sequence listing in electronic form
7. ☐ tables in electronic form related to a sequence listing
8. ☒ other *(specify)*: CHANGE OF ADDRESS

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

Agent: ______________
Gal Ehrlich

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.

   ☐ The applicant has been informed accordingly.

4. ☐ The date of receipt of the demand is WITHIN the time limit of 19 months from the priority date as extended by virtue of Rule 80.5.

5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

6. ☐ The date of receipt of the demand is AFTER the expiration of the time limit under Rule 54*bis*.1(a) and item 7 or 8, below, does not apply.

7. ☐ The date of receipt of the demand is WITHIN the time limit under Rule 54*bis*.1(a) as extended by virtue of Rule 80.5.

8. ☐ Although the date of receipt of the demand is after the expiration of the time limit under Rule 54*bis*.1(a), the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

Application Number: PCT/IL06/00059

Title: **MULTI-DIMENSIONAL IMAGE RECONSTRUCTION AND ANALYSIS FOR EXPERT-SYSTEM DIAGNOSIS**

Applicant: Spectrum Dynamics LLC

Filing Date: January 15, 2006

LETTER ACCOMPANYING DEMAND UNDER CHAPTER II (PCT) AND AMENDMENT UNDER ARTICLE 34 (PCT)

This letter and amendment are filed in response to a search report and accompanying written opinion of the International Searching Authority dated October 10, 2006.

Claims 1, 2 and 10 have been amended, replacement sheets for the claims are attached.

Applicants further attach replacement sheets 2, 8, 14, 15 and 102 to correct typographical errors in numbered lists in the specification.

The Written Opinion indicated that claims 1-17 lack novelty under PCT Article 33(2) in view of US 2003/0208117 to *Shwartz et al.* Applicant respectfully disagrees with this indication, as not all of the limitations of these claims are taught by *Shwartz.*

The independent claims are 1, 2, 5, 6, 10, 11 and 15.

Claim 1 describes a method of image reconstruction of a multi-isotope source. Applicants submit that *Shwartz* does not teach image reconstruction of multi-isotope sources, but rather of a single source. Claim 1 was amended to make it clearer that the photon scatter modeling and reconstruction is for each of a plurality of isotopes. In addition, *Shwartz* does not teach iterative reconstruction as required by the claim.

Claim 2 was amended to make explicit what was already implicit, namely that the determination of the preferred administration dose of the radiopharmaceutical agent is based on the measured distribution of the radiopharmaceutical in the body. Applicant submits that *Shwartz* does not teach or suggest this limitation. *Shwartz* teaches reconstructing an image of a spatial distribution of a pharmaceutical substance, however, there is no mention in *Shwartz* to "determining the preferred administration dose of the radiopharmaceutical agent for at least one future administration based on the measured distribution." As required by the claim. In

addition, *Shwartz* does not suggest "administering a radiopharmaceutical at no more than one fifth of an expected effective dose".

Claims 5, 6, 11 and 15 recite a method or a system and include the limitation of "automatically diagnosing a pathology of the patient, by automatically matching the at least two parameters and the pathological signatures". It is believed by applicants that *Schwartz* does not teach or describe automatic diagnosis by using the previously defined signature as required by this limitation in the claims. In contrast to the claims in the application, it is noted by *Schwartz* in the background (paragraph 0002) that a physician can determine how a particular organ or system is functioning based on the reconstructed image. The object of the invention is stated in paragraph 0006 as providing a technique for reconstruction of such images. Thus, the object of the invention in *Schwartz* is to provide a reconstructed image to the physician for his diagnosis, there is no mention or suggestion of automatic diagnosing by the system.

Claim 10 has been amended to make explicit what was already implicit. The claim now defines a storage medium which includes "a set of machine instructions for associating the at least one radiopharmaceutical kinetic parameter with a disease signature". *Shwartz* does not teach this limitation. *Shwartz* does not relate to kinetic parameters. Moreover, as noted above, the association of the any parameter with a disease signature, if any, in *Shwartz* is performed by the physician and not by the system.

The Search Report also indicates US 6,420,711 to *Tumer* as relevant to the novelty and inventive step of claims 1-17 in the application. *Tumer* describes a method and apparatus for radiation detection. *Tumer* does not teach or suggest image reconstruction of a multi-isotope source as required by claim 1 in the application. In addition, applicants submit that like *Schwartz* referred to above, *Tumer* does not include the limitation of "automatically diagnosing a pathology of the patient, by automatically matching the at least two parameters and the pathological signatures" as required by the rest of the claims in the application. In fact, *Tumer* does not relate to diagnosing at all. If the Examiner is still of the opinion that the limitations of the claims are taught in *Tumer*, the Examiner is respectfully requested to refer to the relevant sections in *Tumer*.

The following documents were referred to in the Search Report as relevant to the inventive step of the claims in the application. US 6,628,984 to *Weinberg* and US 6,135,955 to *Madden* et al. Applicants respectfully submit that neither one of these

documents teach automatic diagnosing or multi source. *Madden* teaches determining the depth of a tissue of known density and provides the practitioner with information to localize the suspected tumor (see Col. 23, line 66 through Col. 24, line 29). However, *Madden* does not teach iterative reconstruction of the image as required by claim 1 or automatic diagnosing a pathology of the patient, as required by the rest of the claims.

Therefore, Applicant believes that none of the documents appearing in the Search Report describe the apparatuses or methods of the present application, including all the limitations of the claims. Applicant respectfully requests that if the IPEA does not intend to issue a positive IPER, based on the arguments and/or amendments submitted herewith, that it give applicant an opportunity to put the application in order for a positive IPER by issuing a further written opinion.

Respectfully submitted,

Dr. Gal Ehrlich
Agent for Applicant

annihilation takes place. As such, PET imaging collects emission events, which occurred in an imaginary tubular section enclosed by the PET detectors. A gold standard for PET imaging is PET NH_3 rest myocardial perfusion imaging with N-13-ammonia (NH_3), at a dose level of 740 MBq, with attenuation correction ~~{XXXX correct}~~. Yet, since the annihilation gamma is of 0.511 Mev, regardless of the radio-isotope, PET imaging does not provide spectral information, and does not differentiate between radio-isotopes.

In SPECT imaging, primarily gamma emitting radio-isotopes are used for labeling, and the imaging camera is designed to detect the actual gamma emission, generally, in an energy range of approximately 11- 511 KeV. Generally, each detecting unit, which represents a single image pixel, has a collimator that defines the solid angle from which radioactive emission events may be detected.

Because PET imaging collects emission events, in the imaginary tubular section enclosed by the PET detectors, while SPECT imaging is limited to the solid collection angles defined by the collimators, generally, PET imaging has a higher sensitivity and spatial resolution than does SPECT. Therefore, the gold standard for spatial and time resolutions in nuclear imaging is defined for PET.

The radiopharmaceutical behavior in vivo is a dynamic process. Some tissues absorb radiopharmaceuticals faster than others or preferentially to others, and some tissues flush out the radiopharmaceuticals faster than others or preferentially to others, so the relative darkness of a given tissue is related to a time factor. Since the uptake clearance of such a radiopharmaceutical by the various tissues (target and background) varies over time, standard diagnosis protocols usually recommend taking an image at the time at which the ratio of target emission versus background emission is the highest.

Yet, this approach produces a single parameter per voxel of the reconstructed image, a level of gray, at a specific time, and ignores the information that could be obtained from the behavior of a radiopharmaceutical as a function of time.

Dynamic imaging, on the other hand, attempts to acquire the behavior of a radiopharmaceutical as a function of time, for example, to measure perfusion in myocardial tissue. Dynamic imaging is advantageous to static imaging, as it provides a better measure of blood flow, it is more sensitive to ischemia than static imaging,

iii. applying algorithm which select a preferred set of views to for ROI focusing, based on the geometry of the organ to be imaged;

iv. zooming in, by a second algorithm tic iteration, to select a preferred set of views based on earlier findings;

v. active vision, which ensures that each detector obtains the maximum information from any position;

6. calibration sources, which may be placed on the body, within a body lumen, or near the camera;

~~11~~7. the use of the calibration sources of (6) to obtain an attenuation map;

~~12~~8. ultrasound-based, or MRI based attenuation correction (~~our 26137~~PCT/IL03/00917, filed November 4, 2003);

~~13~~9. ultrasound-based attenuation correction using ultrasound patches, such as patch-sensor devices, described in U.S. Patents 5,807,268; 5,913,829 and 5,885,222, all of which are assigned to MedAcoustics, Inc., Raleigh, NC, USA, both for structural mapping, for correlating the structural map with the functional map, and for attenuation correction. The ultrasound patches may be incorporatred with the radiopharmaceutical calibration sources;

~~14~~10. minimal multiplexing between the detectors and the analyzer, to prevent saturation;

~~15~~11. customizing to the patient imaging parameters such as overall camera configuration, angular travel of each sweep, sweeping speed, translational travel, angular and (or) translational steps, total imaging time, and the like.

The camera sensitivity may be determined by at least one of the following:

1. a sensitivity in terms of speed of data collection and spatial resolution, at least as good as a gold standard for PET imaging for at rest myocardial perfusion with N-13-ammonia (NH_3);

2. a sensitivity sufficient for reconstructing an image under a Cobalt wire Nema test of a line source of 5 mCi cobalt with a line spread function of less than 7 mm Full Width Half Maximum (FWHM) through air at a distance of at least 100 mm;

3. a sensitivity sufficient for resolving through air at a distance of at least 100 mm under a Nema Bar Phantom test of gaps formed between 1 mm wide led bars positioned less than 7 mm apart from one another over a uniform cobalt disc;

account toxicity, radiation dose, clearance rate, uptake rate by an organ, or any other measurements, as provided by the first administration, to weigh benefit and potential harm.

The effects, which were combined to increase the camera's sensitivity and resolutions, are as follows:

1. solid collection angles greater than 0.1 or 0.15 steradians;
2. close proximity of the detectors to the body, in order to increase both:
   i. detection efficiency, which falls as a proportionally to the square of the distance from an object; and
   ii. resolution, where the number of detector pixels which view an object also falls proportionally to the square of the distance from the object;
3. windshield-wiper sweeping motions, with a center of rotation outside the patient's body, to maximize the information obtained from each x;y;z detector position;
4. trio-vision of each voxel, wherein each voxel is viewed with x, y, and z, components, as opposed to stereo vision in a plane, with only x and y components of state-of-the-art cameras;
5. Focus on a region of interest, by:
   i. prescanning;
   ii. independent motion of detectors, for independent focusing on ROI, by each detector;
   iii. applying algorithm which select a preferred set of views to for ROI focusing, based on the geometry of the organ to be imaged;
   iv. zooming in, by a second algorithm tic iteration, to select a preferred set of views based on earlier findings;
   v. active vision, which ensures that each detector obtains the maximum information from any position;
6. calibration sources, which may be placed on the body, within a body lumen, or near the camera;

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2. a sensitivity sufficient for reconstructing an image under a Cobalt wire Nema test of a line source of 5 mCi cobalt with a line spread function of less than 7 mm Full Width Half Maximum (FWHM) through air at a distance of at least 100 mm;

3. a sensitivity sufficient for resolving through air at a distance of at least 100 mm under a Nema Bar Phantom test of gaps formed between 1 mm wide led bars positioned less than 7 mm apart from one another over a uniform cobalt disc;

4. a sensitivity operative for image acquisition of a full organ in less than 10 seconds at a spatial resolution, capable of identifying objects not greater than about 7 mm X 7 mm X 7 mm with a signal-to-noise ratio of at least 4 to 1 or better;

5. a sensitivity for detecting at least 1 out of every 5000 emitted photons while allowing a reconstructions of a 3D image with a resolution of not more than 5 mm and energy resolution of not more than 15 %; and

6. having a sensitivity to image a volume of about 5cm diameter located about 150 mm from the detectors, with a total sensitivity of about 1 photons detected out of 65 emitted.

~~17~~12. Use of C-11-Raclopride to target dopamine D2 receptors, for brain imaging of dopamine D2 receptors in schizophrenia, and assessment of dose for neuroleptics.

~~18~~13. Use of I-123-iodobenzamide (IBZM) to target dopamine D2 receptors, for brain imaging of dopamine D2 receptors in schizophrenia, and assessment of dose for neuroleptics.

~~19~~14. C-11-carfentanil to target Mu opioid receptors in brain, with the clinical application of imaging drug addiction.

~~20~~15. Use of C-11-α-methyl-L-tryptophan as a precursor for α-methyl serotonin synthesis and as a substrate for AAAD enzyme, with the clinical application of imaging depression.

~~21~~16. Use of C-115-Hydroxytryptophan as a precursor for serotonin synthesis with the clinical application of imaging neuroendocrine tumors.

~~22~~17. Use of F-18-MPPF to bind to 5-HT1A (5-hydroxytryptamine-1A) serotonin receptors, with the clinical application of imaging depression and epilepsy.

~~23~~18. Use of F-18-Altanserin to bind to 5-HT2A serotonin receptors with the clinical application of imaging depression and epilepsy.

~~24~~19. Use of C-11-Acetate for the study of tricarboxylic acid cycle activity and oxidative metabolism with the clinical application of studying myocardial oxygen metabolism.

~~25~~20. Use of C-11-Palmitate as a precursor for fatty acid metabolism with the clinical application of imaging myocardial metabolism.

~~26~~21. F-18-Fluorodopamine to target presynaptic adrenergic receptors

Protocols for Beta Emitting Radiopharmaceuticals

The following beta emitting radionuclides may be used for diagnostic studies, using a dose of about 1 mCi, using the camera of the present invention: Sm-153 ($T_{1/2}$ 1.95 days), I-131 ($T_{1/2}$ 8.04 days), Cu-67 ($T_{1/2}$ 2.58 days), Lu-177 ($T_{1/2}$ 6.7 days), and Sn-117m ($T_{1/2}$ 13.6 days). These include both long-lived radiopharmaceuticals and radiopharmaceuticals with low abundance gamma.

What is claimed:

1. A method of image reconstruction of a multi-isotope source, comprising:

modeling photon scatter for each of a plurality of isotopes j, based on the Compton scatter equation, relating initial and final photon energies to a Compton scatter angle;

employing an iterative process for generating a solution for the image reconstruction, by describing a probability that an emitted photon of an isotope j, from a voxel u, be detected by a detector t, at an energy bin b.

2. A method for determining a future administration dose, comprising:

i. administering a radiopharmaceutical at no more than one fifth of an expected effective dose;

ii. measuring by SPECT the distribution of the radiopharmaceutical in the body; and

~~iv.~~iii. determining the preferred administration dose of the radiopharmaceutical agent for at least one future administration based on the measured distribution.

3. The method of claim 2, wherein the future administration is of a radiopharmaceutical.

4. The method of claim 2, wherein the future administration is of a therapeutic agent.

5. A method of diagnosing a patient condition, comprising:

defining pathological signatures, each characterized by a unique combination of at least two parameters, which relate to behavior of a radiopharmaceutical in vivo;

measuring the at least two parameters, for a patient, by SPECT imaging; and

automatically diagnosing a pathology of the patient, by automatically matching the at least two parameters and the pathological signatures.

6. A method of diagnosing a patient condition, comprising:

defining pathological signatures, each characterized by a unique combination of at least two patient parameters, at least one of which relating to behavior of a radiopharmaceutical in vivo;

measuring the at least two patient parameters, wherein the at least one patient parameter relating to the behavior of the radiopharmaceutical in vivo is measured by SPECT imaging; and

automatically diagnosing a pathology by automatically matching the at least two patient parameters and the pathological signatures.

7. The methods of claims 5 or 6, wherein automatically diagnosing a pathology comprises automatically diagnosing based on a database of values for normal and diseased populations.

8. The methods of claims 5 or 6, wherein measuring includes measuring at least one radiopharmaceutical kinetic parameter of a flow rate across a tissue membrane.

9. The method of any one of claims 5 or 6, and further including automatically determining the degree of the pathology.

10. An electronic storage medium comprising

at least one radiopharmaceutical identity;

SPECT measured values of at least one radiopharmaceutical kinetic parameter of a flow rate across a tissue membrane, for the radiopharmaceutical, and

a set of machine instructions for associating the at least one radiopharmaceutical kinetic parameter with a disease signature.

11. Apparatus for performing automatic diagnosis, based on SPECT data, comprising a set of instructions for:

defining pathological signatures, each characterized by a unique combination of at least two patient parameters, at least one of which relating to behavior of a radiopharmaceutical in vivo, as measured by SPECT;

measuring the at least two patient parameters, wherein the at least one patient parameter relating to the behavior of the radiopharmaceutical in vivo is measured by SPECT imaging; and

automatically diagnosing a pathology by automatically matching the at least two patient parameters and the pathological signatures.

12. The apparatus of claim 11, wherein automatically diagnosing a pathology comprises automatically diagnosing based on a database of values for normal and diseased populations.

13. The apparatus of claim 11, wherein measuring includes measuring at least one radiopharmaceutical kinetic parameter of a flow rate across a tissue membrane.

14. The apparatus of claim 12, wherein automatically diagnosing includes determining a degree of a pathology.

15. An electronic storage medium comprising a set of instructions for:

defining pathological signatures, each characterized by a unique combination of at least two patient parameters, at least one of which relating to behavior of a radiopharmaceutical in vivo, as measured by SPECT;

measuring the at least two patient parameters, wherein the at least one patient parameter relating to the behavior of the radiopharmaceutical in vivo is measured by SPECT imaging; and

automatically diagnosing a pathology by automatically matching the at least two patient parameters and the pathological signatures.

16. The electronic storage medium of claim 15, wherein automatically diagnosing a pathology comprises automatically diagnosing based on a database of values for normal and diseased populations.

annihilation takes place. As such, PET imaging collects emission events, which occurred in an imaginary tubular section enclosed by the PET detectors. A gold standard for PET imaging is PET NH_3 rest myocardial perfusion imaging with N-13-ammonia (NH_3), at a dose level of 740 MBq, with attenuation correction . Yet, since the annihilation gamma is of 0.511 Mev, regardless of the radio-isotope, PET imaging does not provide spectral information, and does not differentiate between radio-isotopes.

In SPECT imaging, primarily gamma emitting radio-isotopes are used for labeling, and the imaging camera is designed to detect the actual gamma emission, generally, in an energy range of approximately 11- 511 KeV. Generally, each detecting unit, which represents a single image pixel, has a collimator that defines the solid angle from which radioactive emission events may be detected.

Because PET imaging collects emission events, in the imaginary tubular section enclosed by the PET detectors, while SPECT imaging is limited to the solid collection angles defined by the collimators, generally, PET imaging has a higher sensitivity and spatial resolution than does SPECT. Therefore, the gold standard for spatial and time resolutions in nuclear imaging is defined for PET.

The radiopharmaceutical behavior in vivo is a dynamic process. Some tissues absorb radiopharmaceuticals faster than others or preferentially to others, and some tissues flush out the radiopharmaceuticals faster than others or preferentially to others, so the relative darkness of a given tissue is related to a time factor. Since the uptake clearance of such a radiopharmaceutical by the various tissues (target and background) varies over time, standard diagnosis protocols usually recommend taking an image at the time at which the ratio of target emission versus background emission is the highest.

Yet, this approach produces a single parameter per voxel of the reconstructed image, a level of gray, at a specific time, and ignores the information that could be obtained from the behavior of a radiopharmaceutical as a function of time.

Dynamic imaging, on the other hand, attempts to acquire the behavior of a radiopharmaceutical as a function of time, for example, to measure perfusion in myocardial tissue. Dynamic imaging is advantageous to static imaging, as it provides a better measure of blood flow, it is more sensitive to ischemia than static imaging,

iii. applying algorithm which select a preferred set of views to for ROI focusing, based on the geometry of the organ to be imaged;

iv. zooming in, by a second algorithm tic iteration, to select a preferred set of views based on earlier findings;

v. active vision, which ensures that each detector obtains the maximum information from any position;

6. calibration sources, which may be placed on the body, within a body lumen, or near the camera;

7. the use of the calibration sources of (6) to obtain an attenuation map;

8. ultrasound-based, or MRI based attenuation correction (PCT/IL03/00917, filed November 4, 2003);

9. ultrasound-based attenuation correction using ultrasound patches, such as patch-sensor devices, described in U.S. Patents 5,807,268; 5,913,829 and 5,885,222, all of which are assigned to MedAcoustics, Inc., Raleigh, NC, USA, both for structural mapping, for correlating the structural map with the functional map, and for attenuation correction. The ultrasound patches may be incorporatred with the radiopharmaceutical calibration sources;

10. minimal multiplexing between the detectors and the analyzer, to prevent saturation;

11. customizing to the patient imaging parameters such as overall camera configuration, angular travel of each sweep, sweeping speed, translational travel, angular and (or) translational steps, total imaging time, and the like.

The camera sensitivity may be determined by at least one of the following:

1. a sensitivity in terms of speed of data collection and spatial resolution, at least as good as a gold standard for PET imaging for at rest myocardial perfusion with N-13-ammonia (NH_3);

2. a sensitivity sufficient for reconstructing an image under a Cobalt wire Nema test of a line source of 5 mCi cobalt with a line spread function of less than 7 mm Full Width Half Maximum (FWHM) through air at a distance of at least 100 mm;

3. a sensitivity sufficient for resolving through air at a distance of at least 100 mm under a Nema Bar Phantom test of gaps formed between 1 mm wide led bars positioned less than 7 mm apart from one another over a uniform cobalt disc;

account toxicity, radiation dose, clearance rate, uptake rate by an organ, or any other measurements, as provided by the first administration, to weigh benefit and potential harm.

The effects, which were combined to increase the camera's sensitivity and resolutions, are as follows:

1. solid collection angles greater than 0.1 or 0.15 steradians;
2. close proximity of the detectors to the body, in order to increase both:
   i. detection efficiency, which falls as a proportionally to the square of the distance from an object; and
   ii. resolution, where the number of detector pixels which view an object also falls proportionally to the square of the distance from the object;
3. windshield-wiper sweeping motions, with a center of rotation outside the patient's body, to maximize the information obtained from each x;y;z detector position;
4. trio-vision of each voxel, wherein each voxel is viewed with x, y, and z, components, as opposed to stereo vision in a plane, with only x and y components of state-of-the-art cameras;
5. Focus on a region of interest, by:
   i. prescanning;
   ii. independent motion of detectors, for independent focusing on ROI, by each detector;
   iii. applying algorithm which select a preferred set of views to for ROI focusing, based on the geometry of the organ to be imaged;
   iv. zooming in, by a second algorithm tic iteration, to select a preferred set of views based on earlier findings;
   v. active vision, which ensures that each detector obtains the maximum information from any position;
6. calibration sources, which may be placed on the body, within a body lumen, or near the camera;
7. the use of the calibration sources of (6) to obtain an attenuation map;

8. ultrasound-based, or MRI based attenuation correction (PCT/IL03/00917, filed November 4, 2003);

9. ultrasound-based attenuation correction using ultrasound patches, such as patch-sensor devices, described in U.S. Patents 5,807,268; 5,913,829 and 5,885,222, all of which are assigned to MedAcoustics, Inc., Raleigh, NC, USA, both for structural mapping, for correlating the structural map with the functional map, and for attenuation correction. The ultrasound patches may be incorporatred with the radiopharmaceutical calibration sources;

10. minimal multiplexing between the detectors and the analyzer, to prevent saturation;

11. customizing to the patient imaging parameters such as overall camera configuration, angular travel of each sweep, sweeping speed, translational travel, angular and (or) translational steps, total imaging time, and the like.

The camera sensitivity may be determined by at least one of the following:

1. a sensitivity in terms of speed of data collection and spatial resolution, at least as good as a gold standard for PET imaging for at rest myocardial perfusion with N-13-ammonia (NH_3);

2. a sensitivity sufficient for reconstructing an image under a Cobalt wire Nema test of a line source of 5 mCi cobalt with a line spread function of less than 7 mm Full Width Half Maximum (FWHM) through air at a distance of at least 100 mm;

3. a sensitivity sufficient for resolving through air at a distance of at least 100 mm under a Nema Bar Phantom test of gaps formed between 1 mm wide led bars positioned less than 7 mm apart from one another over a uniform cobalt disc;

4. a sensitivity operative for image acquisition of a full organ in less than 10 seconds at a spatial resolution, capable of identifying objects not greater than about 7 mm X 7 mm X 7 mm with a signal-to-noise ratio of at least 4 to 1 or better;

5. a sensitivity for detecting at least 1 out of every 5000 emitted photons while allowing a reconstructions of a 3D image with a resolution of not more than 5 mm and energy resolution of not more than 15 %; and

6. having a sensitivity to image a volume of about 5cm diameter located about 150 mm from the detectors, with a total sensitivity of about 1 photons detected out of 65 emitted.

12. Use of C-11-Raclopride to target dopamine D2 receptors, for brain imaging of dopamine D2 receptors in schizophrenia, and assessment of dose for neuroleptics.

13. Use of I-123-iodobenzamide (IBZM) to target dopamine D2 receptors, for brain imaging of dopamine D2 receptors in schizophrenia, and assessment of dose for neuroleptics.

14. C-11-carfentanil to target Mu opioid receptors in brain, with the clinical application of imaging drug addiction.

15. Use of C-11-α-methyl-L-tryptophan as a precursor for α-methyl serotonin synthesis and as a substrate for AAAD enzyme, with the clinical application of imaging depression.

16. Use of C-115-Hydroxytryptophan as a precursor for serotonin synthesis with the clinical application of imaging neuroendocrine tumors.

17. Use of F-18-MPPF to bind to 5-HT1A (5-hydroxytryptamine-1A) serotonin receptors, with the clinical application of imaging depression and epilepsy.

18. Use of F-18-Altanserin to bind to 5-HT2A serotonin receptors with the clinical application of imaging depression and epilepsy.

19. Use of C-11-Acetate for the study of tricarboxylic acid cycle activity and oxidative metabolism with the clinical application of studying myocardial oxygen metabolism.

20. Use of C-11-Palmitate as a precursor for fatty acid metabolism with the clinical application of imaging myocardial metabolism.

21. F-18-Fluorodopamine to target presynaptic adrenergic receptors

Protocols for Beta Emitting Radiopharmaceuticals

The following beta emitting radionuclides may be used for diagnostic studies, using a dose of about 1 mCi, using the camera of the present invention: Sm-153 ($T_{1/2}$ 1.95 days), I-131 ($T_{1/2}$ 8.04 days), Cu-67 ($T_{1/2}$ 2.58 days), Lu-177 ($T_{1/2}$ 6.7 days), and Sn-117m ($T_{1/2}$ 13.6 days). These include both long-lived radiopharmaceuticals and radiopharmaceuticals with low abundance gamma.

What is claimed:

1. A method of image reconstruction of a multi-isotope source, comprising:

modeling photon scatter for each of a plurality of isotopes j, based on the Compton scatter equation, relating initial and final photon energies to a Compton scatter angle;

employing an iterative process for generating a solution for the image reconstruction, by describing a probability that an emitted photon of an isotope j, from a voxel u, be detected by a detector t, at an energy bin b.

2. A method for determining a future administration dose, comprising:

i. administering a radiopharmaceutical at no more than one fifth of an expected effective dose;

ii. measuring by SPECT the distribution of the radiopharmaceutical in the body; and

iii. determining the preferred administration dose of the radiopharmaceutical agent for at least one future administration based on the measured distribution.

3. The method of claim 2, wherein the future administration is of a radiopharmaceutical.

4. The method of claim 2, wherein the future administration is of a therapeutic agent.

5. A method of diagnosing a patient condition, comprising:

defining pathological signatures, each characterized by a unique combination of at least two parameters, which relate to behavior of a radiopharmaceutical in vivo;

measuring the at least two parameters, for a patient, by SPECT imaging; and

automatically diagnosing a pathology of the patient, by automatically matching the at least two parameters and the pathological signatures.

6. A method of diagnosing a patient condition, comprising:

defining pathological signatures, each characterized by a unique combination of at least two patient parameters, at least one of which relating to behavior of a radiopharmaceutical in vivo;

measuring the at least two patient parameters, wherein the at least one patient parameter relating to the behavior of the radiopharmaceutical in vivo is measured by SPECT imaging; and

automatically diagnosing a pathology by automatically matching the at least two patient parameters and the pathological signatures.

7. The methods of claims 5 or 6, wherein automatically diagnosing a pathology comprises automatically diagnosing based on a database of values for normal and diseased populations.

8. The methods of claims 5 or 6, wherein measuring includes measuring at least one radiopharmaceutical kinetic parameter of a flow rate across a tissue membrane.

9. The method of any one of claims 5 or 6, and further including automatically determining the degree of the pathology.

10. An electronic storage medium comprising

at least one radiopharmaceutical identity;

SPECT measured values of at least one radiopharmaceutical kinetic parameter of a flow rate across a tissue membrane, for the radiopharmaceutical, and

a set of machine instructions for associating the at least one radiopharmaceutical kinetic parameter with a disease signature.

11. Apparatus for performing automatic diagnosis, based on SPECT data, comprising a set of instructions for:

defining pathological signatures, each characterized by a unique combination of at least two patient parameters, at least one of which relating to behavior of a radiopharmaceutical in vivo, as measured by SPECT;

measuring the at least two patient parameters, wherein the at least one patient parameter relating to the behavior of the radiopharmaceutical in vivo is measured by SPECT imaging; and

automatically diagnosing a pathology by automatically matching the at least two patient parameters and the pathological signatures.

12. The apparatus of claim 11, wherein automatically diagnosing a pathology comprises automatically diagnosing based on a database of values for normal and diseased populations.

13. The apparatus of claim 11, wherein measuring includes measuring at least one radiopharmaceutical kinetic parameter of a flow rate across a tissue membrane.

14. The apparatus of claim 12, wherein automatically diagnosing includes determining a degree of a pathology.

15. An electronic storage medium comprising a set of instructions for:

defining pathological signatures, each characterized by a unique combination of at least two patient parameters, at least one of which relating to behavior of a radiopharmaceutical in vivo, as measured by SPECT;

measuring the at least two patient parameters, wherein the at least one patient parameter relating to the behavior of the radiopharmaceutical in vivo is measured by SPECT imaging; and

automatically diagnosing a pathology by automatically matching the at least two patient parameters and the pathological signatures.

16. The electronic storage medium of claim 15, wherein automatically diagnosing a pathology comprises automatically diagnosing based on a database of values for normal and diseased populations.